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Psychosis In “Cognitively Asymptomatic” Elderly Subjects Is Associated with Neuritic Plaque Load, Not Neurofibrillary Tangles

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Abstract

Introduction—Despite having severe Alzheimer's disease (AD) pathology, some individuals remain cognitively asymptomatic (cASYM). To explore non-cognitive manifestations in these cASYM individuals, we aim to investigate the prevalence and pathological substrates of psychosis.

Methods—Data was obtained from the National Alzheimer's Coordinating Center. The Neuropsychiatric Inventory Questionnaire, quick version was used to evaluate presence of psychosis. Subjects with Mini-Mental Status Examination (MMSE) score of ≥ 24 with frequent neuritic plaques (NP) were defined as NPcASYM, and those with Braak&Braak (B&B) stage of neurofibrillary tangles (NFT) of V/VI were defined as NTcASYM (both groups collectively designated cASYM). Logistic regression analysis was used to examine the association between NP and NFT severity and psychosis accounting for potential confounders.

Results—We identified 667 subjects with MMSE score of ≥ 24 , of which 137 were NPcASYM and 96 were NTcASYM. NPcASYM were at significantly higher risk of having psychosis compared with those with moderate or sparse/no NP (OR, 2.47, 95% CI: 1.54–3.96). NTcASYM

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Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

were also at higher risk compared to those with B&B stage I-IV, but the association explained by the effect of Lewy body pathology and microinfarcts.

Discussions—The load of NP may be important substrate of psychosis in individuals who show no gross cognitive symptoms.

Keywords

Alzheimer's disease; Neuropathology; Cognitively Asymptomatic; Neuropsychiatric Symptoms; Delusions; Hallucinations

Introduction

Clinicopathological studies indicate that the severity of Alzheimer's disease (AD) pathology is correlated with greater cognitive and functional decline [1-3], but there is an important discordance. The progressive accumulation of neuritic plaques (NP) and neurofibrillary tangles (NFT) develops before clinical symptoms start to emerge [4, 5], but even with severe underlying AD pathology a significant number of individuals remain cognitively intact, reflecting resilience to the ravages of disease, [6, 7]. It is possible that these subjects manifest other manifestations of AD, including psychotic symptoms, preceding cognitive impairments.

Mild behavioural impairment (MBI) has been used in recent years to describe later-life manifestations of neuropsychiatric symptoms (NPS) in the absence of cognitive deficits or in patients with mild cognitive impairment (MCI) [8]. MBI has been linked to increased risk of developing dementia [8]. Psychosis including both delusions and hallucinations are common and clinically distinct NPS of AD [9]. While previous studies have investigated psychosis in association with cognitive function [10, 11], the pathological correlates of psychosis in patients with MBI has not been investigated. Identification of NPS in the absence of cognitive decline or MCI may allow us to better differentiate the neurobiology of these common deficits.

The aim of the current study is to examine the substrate of psychotic symptoms in cognitively intact subjects with severe AD pathology, both NP and NFT. Furthermore, we seek to explore the role of other common pathologies including vascular lesions and Lewy body pathology in the clinical manifestation of psychosis among cognitively asymptomatic individuals.

Methods

Data Source

Data was obtained from the National Alzheimer's Coordinating Center (NACC). The NACC encompasses data from 34 past and present Alzheimer's Disease Centers (ADC). Both the uniform and neuropathology dataset collected between September 2005 and December 2015 were obtained for analysis. The UDS was used to collect demographic and clinical characteristics, and the neuropsychiatric profile based on the Neuropsychiatric Inventory Questionnaire, quick version (NPI-Q), which evaluates neuropsychiatric symptoms within

the last month prior to clinical visit. It is important to note that the criteria for delusions on the NPI-Q is mainly persecutory delusions. The neuropathology dataset provided information on the density of NP and extent of NFT. The density of NP was classified as sparse, moderate, or frequent NP based on the CERAD criteria [12]. The NFT was classified based on Braak & Braak (B&B) stage of NFT, which include B&B stage I or II, B&B stage III or IV, and B&B stage V or VI [13]. The presence of vascular lesions, including absence or presence of microinfarcts, lacunes, and subcortical arteriosclerotic leukoencephalopathy were also obtained. Presence of lacunes was defined as having one or more lacunes (small artery infarcts and/or hemorrhages). Presence of Lewy body pathology was defined as having brainstem, transitional, including amygdala, or diffuse Lewy bodies [14]. Lewy bodies in the olfactory bulb or regions unspecified were not considered.

Subject Criteria

The time interval between last clinical visit and death was limited to two years. Subjects with symptoms of delusions or hallucinations at any point during the course of their illness were categorized as having psychosis. Delusions and hallucinations were not analyzed separately due to limited sample size.

Based on criteria reported in the current literature, subjects with Mini-Mental Status Examination (MMSE) scores of 24 or above were categorized as being cognitively intact [15-17]. Within these groups, subjects with frequent neuritic plaques based on CERAD score of frequent neuritic plaques were classified as NPcASYM, and those with B&B stage V or VI were classified NTcASYM (collectively cASYM). Each group was compared to cognitively intact subjects with absent/low or intermediate load of NP and NFT, respectively. The analyses were replicated using the global Clinical Dementia Rating (CDR) score of 0 or 0.5 (i.e., no impairment or questionable impairment) (Supplemental Table 1).

Subjects with the following primary pathological diagnoses were excluded: amyotrophic lateral sclerosis, prion disease, trinucleotide disease (i.e., Huntington disease, spinocerebellar ataxia, other), malformation of cortical development, white matter disease (i.e., multiple sclerosis or other demyelinating disease), neoplasm (primary and metastatic), frontotemporal lobar degeneration (FTLD) with tau pathology.

Statistical Analysis

The relationship between variables was studied using descriptive statistics. For categorical data, the χ^2 test was used. For continuous data, the Kolmogorov-Smirnov test of normality was first used to evaluate the normality. The independent sample t-test or Mann-Whitney test was used for data with normal or non-normal distribution respectively. The cASYM group was analyzed with respect to the NP density (sparse, moderate or frequent) and the NFT category (dichotomized as: B&B stage I or II, B&B stage III or IV, and B&B stage V or VI). The relationship between NPcASYM or NTcASYM status and psychosis was investigated by fitting logistic regression models, sequentially adjusting for age, sex and educational status (Model B), the additional effect of presence of Lewy body pathology and microinfarcts (Model C); and the effect of AD pathology (Model D). The association is reported as Odds ratios with 95% confidence intervals (CI). Statistical analysis was

performed using SPSS version 23.0 (SPSS Inc., Chicago, IL). The significance level was set at $\alpha=0.05$.

Results

Subject Demographics

On the NACC database, 3835 subjects had autopsy data, and 3106 had autopsy performed within two years of last clinical visit. Of these subjects, 2032 had MMSE score available, of which 736 subjects had MMSE score of equal or greater than 24. Of 736 subjects, 708 had NPI-Q score available, and 3 were missing AD pathology data, and 38 were excluded due to other pathological diagnoses. In total, 667 subjects were included. Further categorization of subjects in different categories of AD pathology are displayed in Figure 1. Not all subjects with AD pathology data had record on vascular lesions (i.e., microinfarcts ($n = 665$), lacunes ($n = 587$), subcortical arteriosclerotic leukoencephalopathy ($n = 586$), Lewy body pathology ($n = 646$)).

Table 1 compares the demographic and clinical characteristics of the cASYM group by NP density and NFT categories. An inverse relation was noted between MMSE score and NP density and NFT category, with lower MMSE score more likely with higher NP density or higher NFT category ($p < 0.05$).

Psychosis in Cognitively Asymptomatic Subjects

Table 2 shows the distribution of the severity of AD pathology, vascular lesions, and Lewy body pathology according to psychosis status. Although not included in the analysis, the sample size for subjects with both delusions and hallucinations are also shown. The percentage distribution of psychotic subjects was highest in the category with frequent NP compared to the category with moderate or sparse/no NP (20% vs. 8% vs. 10%, $p < 0.05$). The differences between psychotic and non-psychotic subjects in the distribution of NFT, microinfarcts, lacunes, subcortical arteriosclerotic leukoencephalopathy, and Lewy body pathology did not reach statistical significance.

Table 3 shows the results from the regression analysis. In unadjusted analysis (Model A), NPcASYM were at significantly higher risk of having psychosis, compared with those with moderate or sparse/no NP (OR, 2.47, 95% CI: 1.54 – 3.96). Adjusting for clinical confounders had marginal impact on the strength of the association (OR, 2.55, 95% CI: 1.58 – 4.11). Further adjustment for Lewy body pathology and microinfarcts had a slight effect on the association with the OR reduced from 2.55 to 2.26. Adjusting for the additional effect of B&B stage, reduced the OR to 2.13, 95% CI: 1.09 – 4.17. In the unadjusted analysis, NTcASYM were at significantly higher risk of psychosis compared to their counterparts who were B&B stage I-III (OR, 1.88, 95% CI: 1.05 – 3.38). Adjusting for demographic confounders had no effect on the strength of the association (OR, 1.89, 95% CI: 1.05 – 3.42). However, further adjustment for Lewy body pathology and microinfarcts resulted to a loss of the association (OR, 1.75, 95% CI: 0.87 – 3.52).

Discussion

Clinicopathological studies investigating the correlation between AD pathology and cognitive status demonstrated a differential effect of NFT and NP. NFT have been identified as prominent indicator of cognitive decline [18-20]. Findings from the present study suggest that NP may be important predictors of non-cognitive clinical manifestations, specifically psychosis. The association between NP and psychosis was independent of demographic factors, vascular pathology, and the severity of NFT. Vascular lesions have been previously identified as a major risk factor for psychosis in AD through clinicopathological and neuroimaging studies [21-23]. Furthermore, Lewy body pathology is a known risk factor for hallucinations [24]. The results of our study did not show an independent association between vascular lesions and Lewy bodies on psychosis. While an association between NFT and psychosis was observed, this association was dependent on effect of vascular lesions and Lewy bodies. However, as our study was cross-sectional, further longitudinal studies may allow for better differentiate the role of NFT, vascular lesions, and Lewy bodies in the manifestation of psychosis. Furthermore, while a significant correlation was found between the MMSE scores in cASYM subjects with severe compared to mild AD pathology, the difference in the scores are clinically negligible.

The present study has several limitations. First of all, delusions and hallucinations were not analyzed separately due to limited sample size. As previous studies have suggested different neurobiology behind delusions and hallucination, further studies are needed to investigate whether NP have differential effect on inducing delusions and hallucinations in cognitively intact subjects [25]. Another important limitation is that we used an arbitrary cut-off MMSE score of 24 to define cognitively intact subjects. This cut-off is considered clinically appropriate and has been frequently used in previous studies, but does not capture subtle cognitive deficits. [15-17]. Therefore, our subject sample does not exclude MCI. Also, missing data might have caused attrition bias, potentially confounding our results. Further studies using a more extensive cognitive examination and complete data on AD pathology is needed to confirm our findings.

In conclusion, this study has demonstrated that in cognitively asymptomatic subjects, AD pathology specifically the severity of NP is associated with higher risk of psychosis. Going forward, longitudinal studies examining the progression of NP and other risk factors may be needed to better understand the neurobiology leading to the divergence in clinical manifestations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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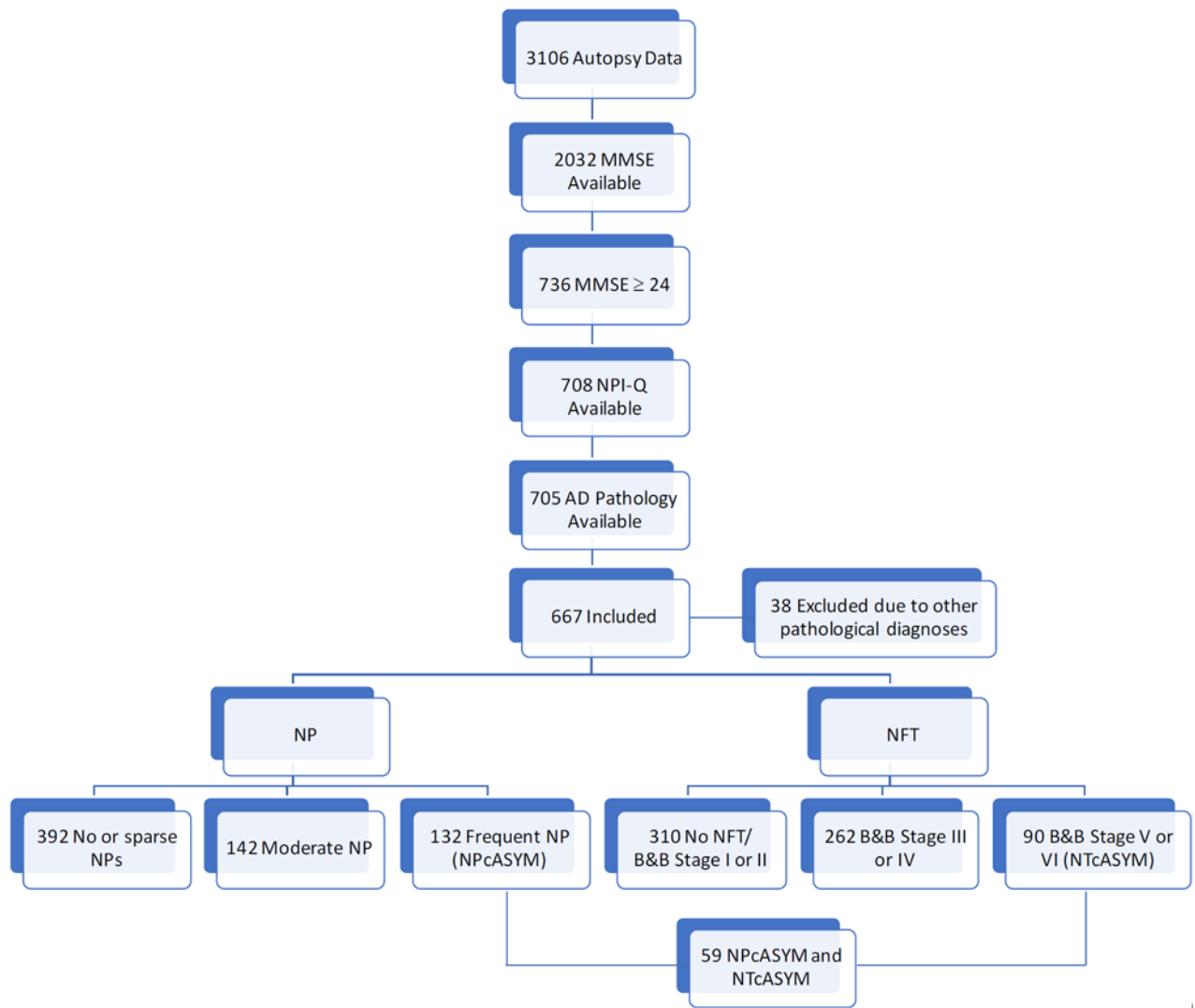


Figure 1. Flow diagram of included participants. MMSE, Mini-Mental State Examination; NPI-Q, Neuropsychiatric Inventory Questionnaire, quick version; NP, Neuritic plaques; NFT, Neurofibrillary tangles

Table 1

Demographic and Clinical Characteristics.

	NP						NFT					
	No or Sparse NPs		Moderate NPs		Frequent NPs		No NFTs or B&B Stage I or II		B&B Stage III or IV		B&B Stage V or VI	
	N / Mean	% /SD	N / Mean	% /SD	N / Mean	% /SD	N / Mean	% /SD	N / Mean	% /SD	N / Mean	% /SD
	N = 392		N = 142		N = 132		N = 310		N = 262		N = 90	
Age at Last Clinical Visit	82.36	11.17	85.35 *	8.65	82.72	8.61	79.73	11.32	86.76 *	7.79	83.53 *	9.15
Age at Death	83.23	11.14	86.10 *	8.59	83.59	8.53	80.60	11.32	87.57 *	7.68	84.39 *	9.09
Interval Between Last Clinical Visit and Death	10.26	5.78	9.71	5.76	10.52	5.68	10.25	5.96	10.24	5.71	10.24	5.33
Sex												
Male	199	51%	84	59%	71	54%	172	55%	128	48%	54	60%
Education (Years)	15.48	2.73	15.84	3.02	16.01	3.02	15.69	2.76	15.40	2.96	16.40	2.81
MMSE Score	27.61	1.86	27.14	1.88	26.73 *	1.92	27.74	1.91	27.24 *	1.82	26.28 *	1.92

NP, neuritic plaques; NFT, neurofibrillary tangles; B&B stage, Braak and Braak stage of NFT; MMSE, mini mental state examination.

Moderate and frequent NP group was independently analyzed against no or sparse NP. B&B stage III or IV or stage V or VI group was independently analyzed against no NFT or stage I or II.

* p < 0.005, Bonferroni correction for multiple comparisons.

Distribution psychosis and severity of Alzheimer’s disease pathology, vascular lesions, and Lewy body pathology.

Table 2

	Never Psychotic		Psychotic		Delusions		Hallucinations	
	N	%	N	%	N	%	N	%
NP								
No or Sparse NP	353	90%	39	10%	30	8%	18	5%
Moderate NP	131	92%	11	8%	7	5%	4	3%
Frequent NP	106	80%	26	20%	22	17%	9	8%
NFT								
No NFT or B&B Stage I or II	280	90%	30	10%	22	7%	13	4%
B&B Stage III or IV	231	88%	31	12%	25	10%	12	5%
B&B Stage V or VI	75	83%	15	17%	12	14%	6	7%
Microinfarcts								
Absent	459	89%	59	11%	45	9%	23	5%
Present	132	89%	17	11%	14	10%	8	6%
Lacunae								
Absent	435	90%	47	10%	37	8%	18	4%
Present	95	87%	14	13%	11	10%	6	6%
Subcortical arteriosclerotic leukoencephalopathy								
Absent	25	86%	4	14%	3	11%	2	7%
Present	33	77%	10	23%	7	18%	4	11%
Lewy Body Pathologies								
Absent	476	90%	54	10%	42	8%	18	4%
Present	98	84%	19	16%	14	13%	12	11%

NP, neuritic plaques; NFT, neurofibrillary tangles; B&B stage, Braak and Braak stage of NFT.

Table 3

Results of regression analysis of the relationship between AD pathology and psychosis in cognitively asymptomatic subjects

Predictor	Model A	Model B	Model C	Model D
NPcASYM				
No	-	-	-	-
Yes	2.47 (1.54 – 3.96)	2.55 (1.58 – 4.11)	2.26 (1.25 – 4.08)	2.13 (1.09 – 4.17)
NTcASYM				
No				
Yes	1.88 (1.05 – 3.38)	1.89 (1.05 – 3.42)	1.75 (0.87 – 3.52)	1.16 (0.52 – 2.58)

Model A: Unadjusted effect

Model B: Adjusted for Age, Sex and years of education

Model C: Model B + Lewy body, microinfarcts

Model D: Model C + B&B stage (for NPcASYM effect analysis) or (NP frequency for NTcASYM effect analysis)